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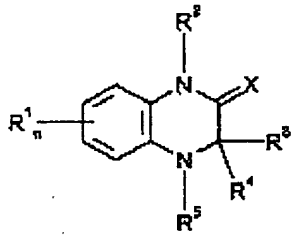
(12) **Patent Application:** (11) **CA 2170222**

(54) USE OF QUINOXALINES IN COMBINATION WITH PROTEASE INHIBITORS AS MEDICAMENTS FOR TREATING AIDS AND/OR HIV INFECTIONS

(54) UTILISATION DE QUINOXALINES COMBINEES AVEC DES INHIBITEURS DE PROTEASE, COMME MEDICAMENTS POUR LE TRAITEMENT DU SIDA ET (OU) D'AUTRES INFECTIONS PAR LE VIH

Representative Drawing:



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ABSTRACT:
The present invention relates to the use of quinoxalines in combination with protease inhibitors as medicaments for treating AIDS and/or HIV infections.

CLAIMS: Show all claims

*** Note: Data on abstracts and claims is shown in the official language in which it was submitted.

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2170222

Use of quinoxalines in combination with protease inhibitors as medicaments for treating AIDS and/or HIV infections

Abstract

The present invention relates to the use of quinoxalines in combination with protease inhibitors as medicaments for treating AIDS and/or HIV infections.

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Use of quinoxalines in combination with protease inhibitors as medicaments for treating AIDS and/or HIV infections

The present invention relates to the use of quinoxalines in combination with protease inhibitors as medicaments for treating AIDS and/or HIV infections.

The human immunodeficiency virus (HIV) causes a persistent, progressive, chronic disease. HIV destroys the immune system (acquired immunodeficiency syndrome, AIDS) and the central and peripheral nervous system. In addition to this, a large number of other clinical manifestations encompassed within the ARC/AIDS syndrome are caused by the human immunodeficiency virus - in particular opportunistic infections (O.I.) which are elicited by other viruses, such as, for example, herpes viruses (HSV I and II) and cytomegalovirus (CMV), or O.I. which are elicited by bacteria, fungi or parasites.

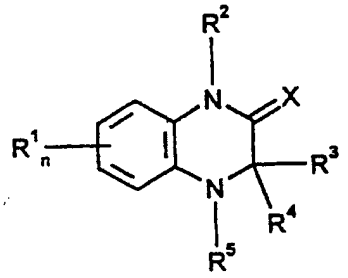
HIV belongs to the retrovirus family; one of the important enzyme activities of these viruses, which is essential for the replication cycle, is that of the protease (Huff, J.R., J. Med. Chem. (1991), 34, 2305-2314). Small molecular weight analogues, of a peptide or non-peptide nature, of the natural substrates of the protease inhibit HIV replication (Roberts, N.A. et al., Science (1990) 248, 358 - 361; Lam, P.Y.S. et al., Science (1994), 263, 380-384).

Analogues of the natural substrates of the reverse transcriptase such as, for example, azidothymidine (AZT), dideoxycytidine (DDC), dideoxyinosine (DDI) and 3'-thiacytidine (Lamivudine) inhibit HIV replication in vitro and in vivo. AZT is used, for

example, for treating ARC/AIDS patients. However, the long-term therapeutic treatment of HIV-infected patients with AZT is accompanied by bone marrow toxicity; in addition to this, AZT-resistant virus isolates develop. Intolerances, such as, for example, a peripheral neuropathy, are reported by some patients who have been treated with DDC or DDI. There is, therefore, a need for new inhibitors which will provide a well-tolerated and effective therapy.

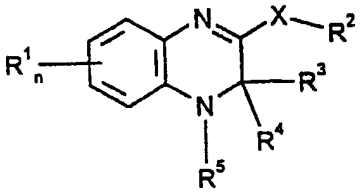
The combination of quinoxalines and protease inhibitors which has now been found is novel, and the synergistic effect of these compounds on HIV replication, when they are used in controlling AIDS or HIV infections, represents a considerable improvement as compared with the state of the art.

It has now been found that quinoxalines of the general formulae (I) and (Ia)



(I)

and also their tautomeric forms of the general formula Ia



(Ia)

in which

1) n is zero,
one,
two,
three
or four,

the individual substituents R^1 are, independently of each other,

fluorine, chlorine, bromine, iodine, trifluoromethyl, trifluoromethoxy, hydroxyl, C_1-C_8-alkyl, C_5-C_8-cycloalkyl, C_1-C_6-alkoxy, (C_1-C_6-alkoxy)-(C_1-C_4-alkoxy), C_1-C_6-alkylthio, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, nitro, amino, azido, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, piperidino, morpholino, 1-pyrrolidinyl, 4-methylpiperazinyl, thiomorpholino, imidazolyl, triazolyl, tetrazolyl, C_1-C_6-acyl, C_1-C_6-acyloxy, C_1-C_6-acylamino, cyano, carbamoyl, carboxyl, (C_1-C_6-alkyl)-oxycarbonyl, hydroxysulphonyl or sulphamoyl,

or

a phenyl, phenoxy, phenoxycarbonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, phenoxysulphonyl, phenylsulphonyloxy, anilinosulphonyl, phenylsulphonylamino, benzoyl, 2-pyridyl, 3-pyridyl or 4-pyridyl radical which is substituted by up to five R^6 radicals which are independent of each other,

where R^6

can be fluorine, chlorine, bromine, iodine, cyano, trifluoromethyl, trifluoromethoxy, nitro, amino, azido, C_1-C_6-alkyl, C_3-C_8-cycloalkyl, C_1-C_6-alkoxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, (C_1-C_6-alkyl)-oxycarbonyl, phenyl, phenoxy or 2-, 3- or 4-pyridyl,

R^2 and R^5 are identical or different and are, independently of each other,

hydrogen, hydroxyl, C_1-C_6-alkoxy, aryloxy, C_1-C_6-acyloxy, cyano, amino, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, arylamino, C_1-C_6-acylamino, C_1-C_8-alkyl, optionally substituted by fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_2-C_8-alkenyl,
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-allenyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;
C_3-C_8-alkinyl,
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-cycloalkyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-cycloalkenyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

(C_3-C_8-cycloalkyl)-(C_1-C_4-alkyl)
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-

acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

(C_3-C_8-cycloalkenyl)-(C_1-C_4-alkyl)
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_1-C_6-alkylcarbonyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_2-C_8-alkenylcarbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_3-C_8-cycloalkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_5-C_8-cycloalkenyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_3-C_8-cycloalkyl)-(C_1-C_3-alkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_5-C_6-cycloalkenyl)-(C_1-C_3-alkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_8-alkyloxycarbonyl which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino or C_1-C_4-alkylthio;

C_2-C_8-alkenyloxycarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_2-C_8-alkinyloxycarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_8-alkylthiocarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_2-C_8-alkenylthiocarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_8-alkylaminocarbonyl and di(C_1-C_8-alkyl)aminocarbonyl which are optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

pyrrolidin-1-yl, morpholino-, piperidino-, piperazinyl- or 4-methylpiperazin-1-yl-carbonyl which are optionally substituted by C_1-C_4-alkyl, C_2-C_6-alkenyl, C_1-C_4-acyl, oxo, thioxo, carboxyl or phenyl;

C_2-C_8-alkenylaminocarbonyl and di(C_1-C_6-alkenyl)aminocarbonyl which are optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_6-alkylsulphonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_6-alkenylsulphonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

or aryl, arylcarbonyl, aryl(thiocarbonyl), (arylthio)carbonyl, (arylthio)thiocarbonyl, aryloxycarbonyl, arylaminocarbonyl, (arylamino)thiocarbonyl, arylalkylaminocarbonyl, arylsulphonyl, arylalkyl, arylalkenyl, arylalkinyl, arylalkylcarbonyl, arylalkenylcarbonyl, arylalkoxycarbonyl or aryl(alkylthio)carbonyl which are substituted by up to five R^6 radicals which are independent of each other, and where the alkyl radical can in each case contain from 1 to 5 C atoms and R^6 is defined as above

or heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkylcarbonyl or heteroarylalkenylcarbonyl, heteroaryloxycarbonyl, (heteroarylthio)carbonyl, heteroarylaminocarbonyl, heteroarylalkyloxycarbonyl, heteroaryl(alkylthio)carbonyl or heteroarylalkylaminocarbonyl which are substituted by up to three R^6 radicals which are independent of each other, and where the alkyl radical can in each case contain from 1 to 3 C atoms,

R^3 and R^4 are identical or different and are, independently of each other,

hydrogen, or C_1-C_8-alkyl which is optionally substituted by fluorine, chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_2-C_8-alkenyl which is optionally substituted by fluorine or chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_3-C_8-cycloalkyl which is optionally substituted by fluorine, chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_3-C_8-cycloalkenyl which is optionally substituted by fluorine or chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy,

C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;
aryl, arylalkyl, heteroaryl or heteroarylalkyl which are substituted by up to five R^6 radicals which are independent of each other, and where the alkyl radical can in each case contain from 1 to 3 C atoms and R^6 is defined as above,

R^3 and R^4 or R^3 and R^5 can, in addition, also be part of a saturated or unsaturated carbocyclic or heterocyclic ring having from 3 to 8 C atoms which can optionally be substituted by fluorine, chlorine, hydroxyl, amino, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_1-C_6-acyloxy, benzoyloxy, C_1-C_6-alkoxy, oxo, thioxo, carboxyl, carbamoyl or phenyl,

X denotes oxygen, sulphur, selenium or substituted nitrogen N-R^2, in which R^2 can have the abovementioned meanings,

with the exception of the compounds in which R^3 and R^4 simultaneously denote H and compounds in which R^2 and R^5 denote H and R^3 and/or R^4 denote arylalkyl and compounds in which X denotes oxygen and R^2 and R^5 denote hydrogen,

are very well suited, in combination with protease inhibitors, for use as medicaments in the control of AIDS and HIV infections.

The alkyl groups mentioned in the preceding definitions can be straight-chain or branched. Unless otherwise defined, they preferably contain 1-8, particularly preferably 1-6, in particular 1-4, C atoms. Examples are the methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl groups, and the like.

The alkenyl groups mentioned in the preceding definitions can be straight-chain or branched and contain from 1 to 3 double bonds. Unless otherwise defined, these groups preferably contain 2-8, in particular 2-6, C atoms. Examples are the 2-propenyl, 1-methylethenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 3-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 3,3-dichloro-2-propenyl and pentadienyl groups, and the like.

The alkinyl groups mentioned in the preceding definitions can be straight-chain or branched and contain from 1 to 3 triple bonds. Unless otherwise defined, they preferably contain 2-8, particularly preferably 3-6, C atoms. Examples are the 2-propinyl and 3-butinyl groups, and the like.

Unless otherwise defined, the cycloalkyl and cycloalkenyl groups mentioned in the preceding definitions preferably contain 3-8, particularly preferably 4-6, C atoms. Examples are the cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl groups.

The acyl groups mentioned in the preceding definitions can be aliphatic, cycloaliphatic or aromatic. Unless otherwise defined, they preferably contain 1-8, particularly preferably 2-7, C atoms. Examples of acyl groups are the formyl, acetyl, chloroacetyl, trifluoroacetyl, hydroxyacetyl, propionyl, butyryl, isobutyryl, pivaloyl, cyclohexanoyl and benzoyl groups.

The aryl groups mentioned in the preceding definitions are preferably aromatic groups having 6-14 C atoms, in particular having 6-10 C atoms, such as, for example, phenyl and naphthyl.

Examples of suitable heteroatoms in the abovementioned heterocyclic rings or heteroaryl groups are, in particular, O, S and N, where N-Z, in which Z is H or R^5 having the respective, above-described definitions, is present in the case of a N-containing ring which is saturated at this position.

Unless otherwise defined, the heterocyclic rings preferably have 1-13 C atoms and 1-6 heteroatoms, in particular 3-9 C atoms and 1-4 heteroatoms.

Examples of suitable heteroaromatic radicals for the heteroaryl groups mentioned in the preceding definitions are radicals such as 2- or 3-thienyl, 2- or 3-furyl, 2-, 3- or 4-pyridyl, pyrimidyl, indolyl, quinolyl or isoquinolyl.

Examples of the aralkyl groups listed in the preceding definitions are benzyl,

phenylethyl, naphthylmethyl and styryl.

The abovementioned substituents R^1 to R^5 are preferably substituted 3 times, particularly preferably 2 times, in particular once, with the substituents which are given in each case.

The ranges for the individual substituents which were previously described as being preferred are likewise preferred for the respective composite substituent definitions (such as, for example, arylalkoxycarbonyl).

Depending on the different substituents, compounds of the formulae I and Ia can possess several asymmetric carbon atoms.

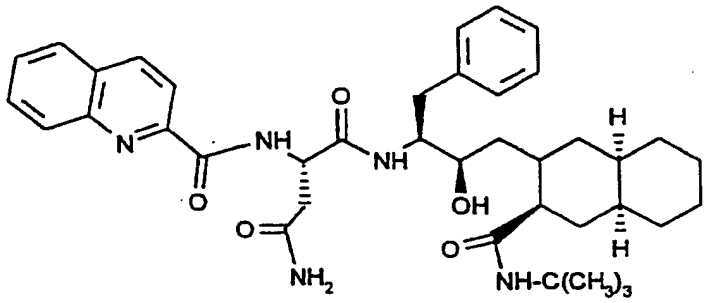
The invention relates, therefore, both to the pure stereoisomers and to mixtures thereof, such as, for example, the affiliated racemate.

The pure stereoisomers of the compounds of the formulae I and Ia can be prepared directly, or resolved subsequently, using known methods or in analogy with known methods.

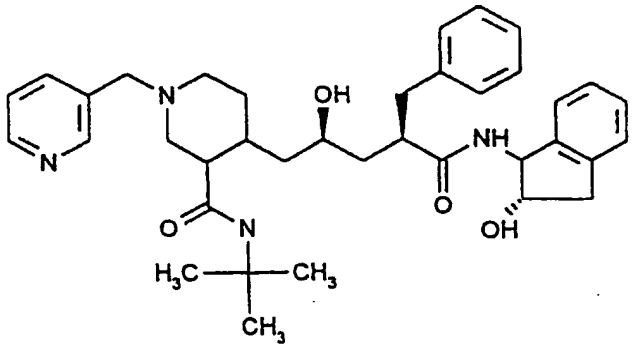
Within the scope of the invention, protease inhibitors denote known peptide analogues of differing structure which are suitable for treating retrovirus-induced diseases.

The following may, in particular, be mentioned:

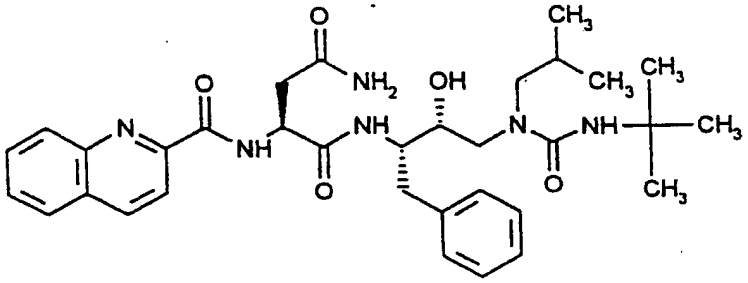
1. (S)-N-[(alphaS)-alpha-[(1R)-2-[((3S,4aS,8aS)-3-(tert-butylcarbamoyl)octahydro-2(1H)-isoquinolinyl)-1-hydroxyethyl)phenethyl-2-quinaldamido]succinamide (EP 432 695 A2)



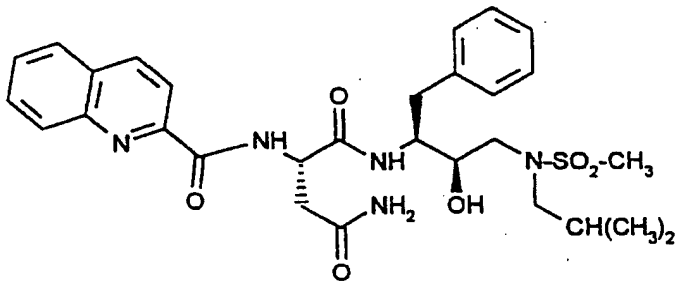
2. 2(R)-Benzyl-5-(2(S)-(N-tert-butylcarbamoyl)-4-(3-pyridylmethyl)piperazin-1-yl)-4(S)-hydroxy-N-(2(R)-hydroxyindan-1(S)-yl)pentanamide (L-735524, EP 569 083 A1, EP 541 168 A1)



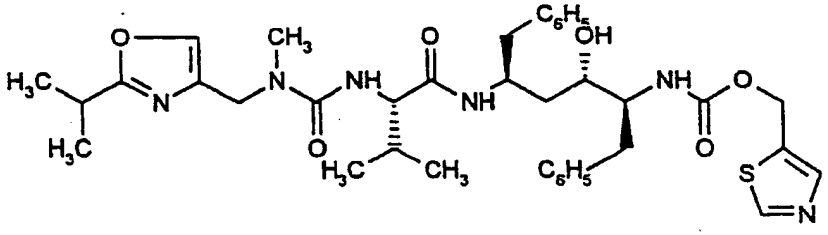
3. N-(Quinolin-2-ylcarbonyl)-asparagine-1(S)-benzyl-3-(3-tert-butyl-1-isobutylureido)-2(R)-hydroxypropylamide (SC 52 151, PCT WO 92/08688 A1, WO 92/08699 A1, WO 92/08698 A1, WO 92/08701 A1, WO 92/08700 A1)



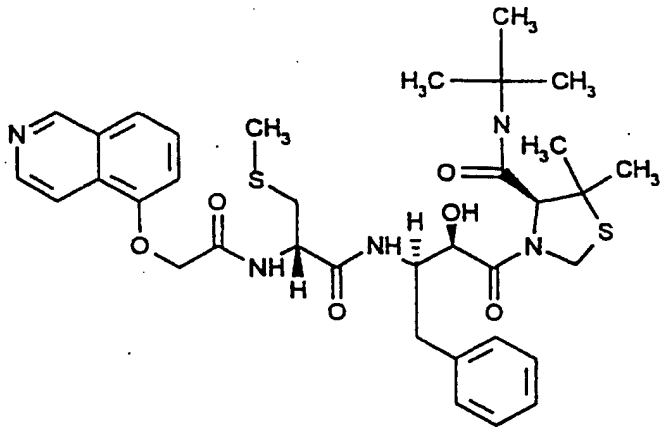
4. N1-(2R-hydroxy-3-((3-methylbutyl)methylsulphonyl)amino)-1S-(phenylmethyl)propyl)-2S-((2-quinolinylcarbonyl)amino)butanediamide (AM 11 686, PCT WO 94/04492)



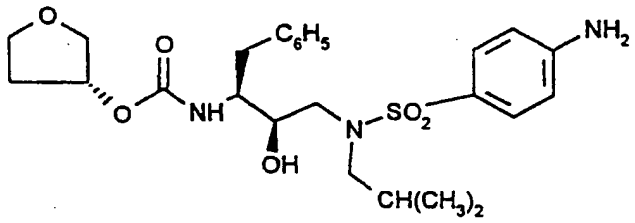
5. (2S,3S,5S)-5(N-(N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (A 84 538, PCT WO 94/14436)



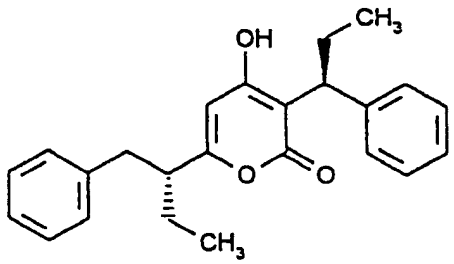
6. (R)-N-tert-butyl-3-((2S,3S)-2-hydroxy-3-N-((R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-methylthiopropanoyl)amino-4-phenylbutanoyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxamide (KNI 272 / Nippon Mining)



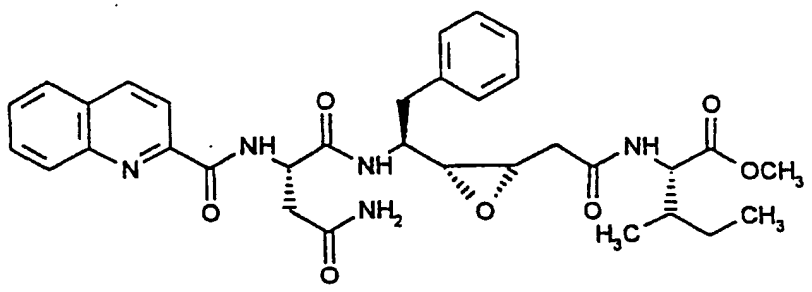
7. {3-[(4-Amino-benzenesulphonyl)-isobutyl-amino]-1-benzyl-2-hydroxypropyl}-carbamic acid tetrahydro-furan-3-yl ester



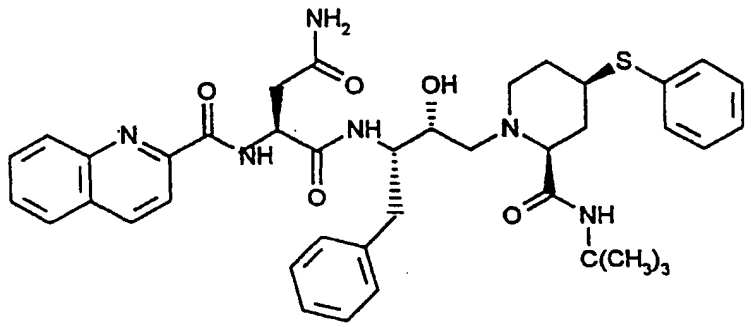
8. (3S,6R)-3-(α-Ethylbenzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one (VB 11 478, PCT WO 9411361)



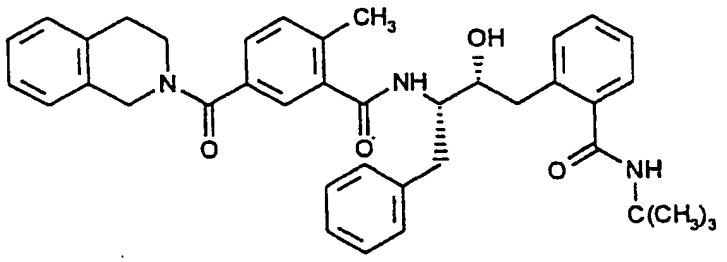
9. N-[5-L-[N-(2-quinolinecarbonyl)-L-asparaginyl]amino-(4R,3S)-epoxy-6-phenyl-hexanoyl]-isoleucine (EP 601 486 A)



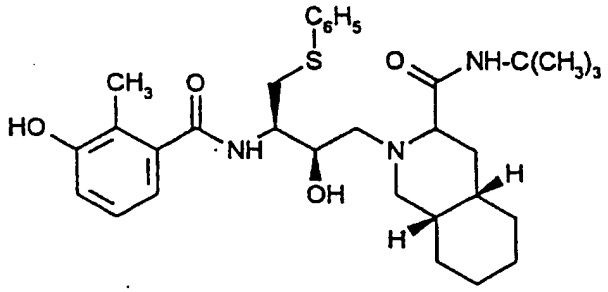
10. N-tert-butyl-1-[2-(R)-hydroxy-4-phenyl)-3(S)-[[N-(2-quinolinylcarbonyl) asparaginyl]amino]butyl-4(R)-(phenylthio)piperidine-2(S)-carboxamide (EP 560 268 A)



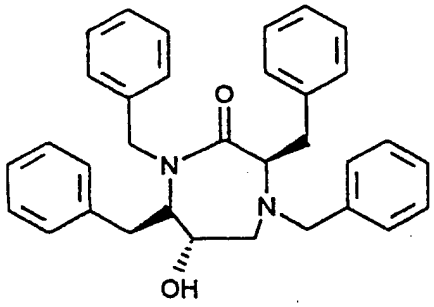
11. [3'''S-(3'''R*,4'''S*)]-N-[1'-oxo-1'-(3''-[1'''-oxo-2'''-aza-3'''-phenylmethyl-4'''-hydroxy-5'''-(2'''-N-tert-butylcarbamido)phenyl]pentyl-4''-methyl)-1,2,3,4-tetrahydroisoquinoline (EP 609 625 A)



12. 2-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenylsulphanylbutyl]-decahydro-isoquinoline-3-carboxylic acid tert-butylamide
(AG 1343 Agouron Pharmaceuticals Inc., San Diego USA)



13. 2H-1,4-Diazepin-2-one,hexahydro-6-hydroxy-1,3,4,7-tetrakis(phenylmethyl)-, [3S'-(3.alpha, 6.beta, 7.beta)] (PCT WO 94/08977)



Quinoxalines of the general formulae (I) and (Ia) are preferred

in which

2) n is zero,
one,
two
or three,

the individual substituents R^1 are, independently of each other,

fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, hydroxyl, C_1-C_4-alkyl, C_5-C_6-cycloalkyl, C_1-C_4-alkoxy, (C_1-C_4-alkoxy)-(C_1-C_4-alkoxy), C_1-C_4-alkylthio, C_1-C_4-alkyl-sulphinyl, C_1-C_4-alkylsulphonyl, nitro, amino, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, piperidino, morpholino, 1-pyrrolidinyl, 4-methyl-piperazinyl, thiomorpholino, imidazolyl, C_1-C_4-acyl, C_1-C_4-acyloxy, C_1-C_4-acylamino, cyano, carbamoyl, carboxyl, (C_1-C_4-alkyl)-oxycarbonyl, hydroxysulphonyl or sulphamoyl,

or

are a phenyl, phenoxy, phenoxycarbonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, phenoxysulphonyl, phenylsulphonyloxy, anilinosulphonyl, phenylsulphonylamino, benzoyl, 2-pyridyl, 3-pyridyl or 4-pyridyl radical which is substituted by up to two R^6 radicals which are independent of each other,

where R^6

can be fluorine, chlorine, bromine, cyano, trifluoromethyl, nitro, amino, C_1-C_4-alkyl, C_3-C_7-cycloalkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, C_1-C_4-alkyl-sulphinyl, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)-amino, (C_1-C_4-alkyl)-oxycarbonyl, phenyl or phenoxy,

R^2 is hydrogen and R^5 is

hydrogen, hydroxyl, cyano, amino, C_1-C_6-alkyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_2-C_8-alkenyl,
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-

acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-allenyl,

C_3-C_8-alkinyl,
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-cycloalkyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-cycloalkenyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

(C_3-C_8-cycloalkyl)-(C_1-C_2-alkyl)
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

(C_3-C_8-cycloalkenyl)-(C_1-C_2-alkyl)
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino,

di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_1-C_6-alkylcarbonyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_2-C_6-alkenylcarbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_3-C_6-cycloalkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_5-C_6-cycloalkenyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_3-C_6-cycloalkyl)-(C_1-C_2-alkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_5-C_6-cycloalkenyl)-(C_1-C_2-alkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_6-alkyloxycarbonyl which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino or C_1-C_4-alkylthio;

C_2-C_6-alkenyloxycarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_2-C_6-alkinyloxycarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_6-alkylthiocarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_2-C_6-alkenylthiocarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_6-alkylaminocarbonyl and di(C_1-C_6-alkyl)aminocarbonyl which are optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

pyrrolidin-1-yl or morpholino-, piperidino-, piperazinyl- or 4-methylpiperazin-1-yl-carbonyl;

C_2-C_6-alkenylaminocarbonyl and di(C_1-C_6-alkenyl)aminocarbonyl which are optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_4-alkylsulphonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_4-alkenylsulphonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

or aryl, arylcarbonyl, aryl(thiocarbonyl), (arylthio)carbonyl, (arylthio)thiocarbonyl, aryloxycarbonyl, arylaminocarbonyl, (arylamino)thiocarbonyl, arylalkylaminocarbonyl, arylsulphonyl, arylalkyl, arylalkenyl, arylalkinyl, arylalkylcarbonyl, arylalkenylcarbonyl, aryl(alkylthio)carbonyl or arylalkoxycarbonyl which are substituted by up to three R^6 radicals which are independent of each other and where the alkyl radical can in each case contain from 1 to 5 C atoms and R^6 is defined as above

or 1- or 2-naphthylmethyl, 2-, 3- or 4-picolyl, 2- or 3-furylmethyl, 2- or 3-thienylmethyl, 2- or 3-pyrrolylmethyl, 2-, 3- or 4-pyridylcarbonyl, 2- or 3-

furylcarbonyl, 2- or 3-thienylcarbonyl, 2- or 3-thienylacetyl, 2-, 3- or 4-picolyloxycarbonyl, 2- or 3-furylmethyloxycarbonyl or 2- or 3-thienylmethyloxycarbonyl which are substituted by up to two R^6 radicals which are independent of each other,

and

R^3 and R^4 are identical or different and are, independently of each other,

hydrogen,

C_1-C_6-alkyl

which is optionally substituted by fluorine, chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_2-C_8-alkenyl which is optionally substituted by fluorine or chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_3-C_8-cycloalkyl which is optionally substituted by fluorine, chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_3-C_8-cycloalkenyl which is optionally substituted by fluorine or chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

or aryl, arylalkyl, heteroaryl or heteroarylalkyl which are substituted by up to three R^6 radicals which are independent of each other, and where the alkyl radical can in each case contain from 1 to 3 C atoms and R^6 is defined as

above,

R^3 and R^4 can, in addition, also be
part of a saturated or unsaturated carbocyclic or heterocyclic ring having from 3 to 7 C atoms which can optionally be substituted by fluorine, chlorine, hydroxyl, amino, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkinyl, C_1-C_4-acyloxy, benzoyloxy, C_1-C_4-alkoxy, oxo, thioxo, carboxyl, carbamoyl or phenyl,

X denotes oxygen, sulphur or selenium

optionally in an isomeric form, in combination with protease inhibitors of the group:

1. (S)-N-[(alphaS)-alpha-[(1R)-2-[((3S,4aS,8aS)-3-(tert-butylcarbamoyl)octahydro-2(1H)-isoquinolinyl)-1-hydroxyethyl)phenethyl-2-quinaldamido]succinamide

2. 2(R)-Benzyl-5-(2(S)-(N-tert-butylcarbamoyl)-4-(3-pyridylmethyl)piperazin-1-yl)-4(S)-hydroxy-N-(2(R)-hydroxyindem-1(S)-yl)pentanamide

3. N-(Quinolin-2-ylcarbonyl)-asparagine-1(S)-benzyl-3-(3-tert-butyl-1-isobutylureido)-2(R)-hydroxypropylamide

4. N1-(2R-hydroxy-3-((3-methylbutyl)methylsulphonyl)amino)-1S-(phenylmethyl)propyl)-2S-((2-quinolinylcarbonyl)amino)butanediamide

5. (2S,3S,5S)-5(N-(N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

6. (R)-N-tert-butyl-3-((2S,3S)-2-hydroxy-3-N-((R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-methylthiopropanoyl)amino-4-phenylbutanoyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxamide

7. {3-[(4-Amino-benzenesulphonyl)-isobutyl-amino]-1-benzyl-2-hydroxypropyl}-carbamic acid tetrahydro-furan-3-yl ester

8. (3S,6R)-3-(α-Ethylbenzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one (VB 11 478, PCT WO 9411361)

9. N-[5-L-[N-(2-quinolinecarbonyl)-L-asparaginyl]amino-(4R,3S)-epoxy-6-phenyl-hexanoyl]-isoleucine

10. N-tert-butyl-1-[2-(R)-hydroxy-4-phenyl)-3(S)-[[N-(2-quinolinylcarbonyl)-asparaginyl]amino]butyl-4(R)-(phenylthio)piperidine-2(S)-carboxamide

11. [3'''S-(3'''R*,4'''S*)]-N-[1'-oxo-1'-(3''-[1'''-oxo-2'''-aza-3'''-phenylmethyl-4'''-hydroxy-5'''-(2'''-N-tert-butylcarbamido)phenyl]pentyl-4''-methyl)-1,2,3,4-tetrahydroisoquinoline

12. 2-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenylsulphanylbutyl]-decahydro-isoquinoline-3-carboxylic acid tert-butylamide

13. 2H-1,4-Diazepin-2-one,hexahydro-6-hydroxy-1,3,4,7-tetrakis(phenylmethyl)-, [3S-(3.alpha, 6.beta, 7.beta)]

for use as medicaments in the treatment of AIDS and/or HIV infections.

Quinoxalines of the general formulae (I) and (Ia) are particularly preferred

in which

n is zero,
one
or two,

the individual substituents R^1 are, independently of each other,

fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, (C_1-C_4-alkoxy)-(C_1-C_2-alkoxy), C_1-C_4-alkylthio, nitro, amino, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, piperidino, morpholino, 1-pyrrolidinyl, 4-methylpiperazinyl, C_1-C_4-acyl, C_1-C_4-acyloxy, C_1-C_4-acylamino, cyano, carbamoyl, carboxyl, (C_1-C_4-alkyl)-oxycarbonyl, hydroxysulphonyl or sulphamoyl,

or

are a phenyl, phenoxy, phenylthio, phenylsulphonyl, phenoxysulphonyl, benzoyl, 2-pyridyl, 3-pyridyl or 4-pyridyl radical which is substituted by up to two R^6 radicals which are independent of each other,

where R^6

can be fluorine, chlorine, bromine, cyano, trifluoromethyl, nitro, amino, C_1-C_4-alkyl, C_1-C_4-alkoxy, (C_1-C_4-alkyl)-oxycarbonyl, phenyl or phenoxy,

R^2 is hydrogen and R^5 is

C_1-C_6-alkyl
which is optionally substituted by C_1-C_4-alkoxy or C_1-C_4-alkylthio;

C_2-C_6-alkenyl,
which is optionally substituted by oxo;

C_3-C_6-allenyl,

C_3-C_8-alkinyl, in particular 2-butinyl;

C_3-C_6-cycloalkyl;

C_5-C_6-cycloalkenyl;

(C_3-C_6-cycloalkyl)-(C_1-C_2-alkyl), in particular cyclopropylmethyl, which is optionally substituted by C_1-C_4-alkyl;

(C_3-C_6-cycloalkenyl)-(C_1-C_2-alkyl), in particular cyclohexenylmethyl;

C_1-C_6-alkylcarbonyl
which is optionally substituted by fluorine, chlorine, hydroxyl, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, C_1-C_4-alkenylamino, di(C_1-C_4-alkyl)amino, 1-pyrrolidinyl, piperidino, morpholino, 4-methylpiperazin-1-yl or C_1-C_4-alkylthio;

C_2-C_6-alkenylcarbonyl;

C_1-C_6-alkyloxycarbonyl which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino or C_1-C_4-alkylthio;

C_2-C_6-alkenyloxycarbonyl, in particular vinyloxycarbonyl, allyloxycarbonyl, isopropenyloxycarbonyl, butenyloxycarbonyl or pentenyloxycarbonyl;

C_2-C_6-alkinyloxycarbonyl, in particular propinyloxycarbonyl or butinyloxycarbonyl;

C_1-C_6-alkylthiocarbonyl;

C_2-C_6-alkenylthiocarbonyl, in particular allylthiocarbonyl;

C_1-C_6-alkylaminocarbonyl and di(C_1-C_6-alkyl)aminocarbonyl;

pyrrolidin-1-yl or morpholino-, piperidino-, piperazinyl- or 4-methylpiperazin-1-yl-carbonyl;

C_2-C_6-alkenylaminocarbonyl and di(C_1-C_6-alkenyl)aminocarbonyl;

C_1-C_4-alkylsulphonyl;

C_1-C_4-alkenylsulphonyl;

or aryl, in particular phenyl,
arylcarbonyl, in particular benzoyl, (arylthio)carbonyl, aryloxycarbonyl, arylaminocarbonyl, (arylamino)thiocarbonyl, arylalkylaminocarbonyl, arylsulphonyl,
arylalkyl, in particular benzyl, phenylethyl, arylalkenyl, arylalkylcarbonyl, arylalkoxycarbonyl or aryl(alkylthio)carbonyl which are substituted by up to two R^6 radicals which are independent of each other and where the alkyl radical can in each case contain from 1 to 3 C atoms and R^6 is defined as above

or 1- or 2-naphthylmethyl, 2-, 3- or 4-picolyl, 2- or 3-furylmethyl, 2- or 3-thienylmethyl, 2- or 3-pyrrolylmethyl, 2-, 3- or 4-pyridylcarbonyl, 2- or 3-furylcarbonyl, 2- or 3-thienylcarbonyl, 2- or 3-thienylacetyl, 2-, 3- or 4-picolyloxycarbonyl, 2- or 3-furylmethyloxycarbonyl or 2- or 3-thienylmethyloxycaronyl which are substituted by up to two R^6 radicals which are independent of each other,

and

R^3 and R^4 are identical or different and are, independently of each other,

hydrogen,
C_1-C_4-alkyl
which is optionally substituted by hydroxyl, mercapto, C_1-C_4-alkoxy, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_2-C_6-alkenyl,

aryl, benzyl, thienyl or thienylmethyl which are substituted by up to two R^6 radicals which are independent of each other and where R^6 is defined as above,

R^3 and R^4 can also be

part of a saturated or unsaturated carbocyclic or heterocyclic ring having from 3 to 6 C atoms which can optionally be substituted by oxo or thioxo, and

X denotes oxygen or sulphur

optionally in an isomeric form in combination with protease inhibitors of the group:

1. (S)-N-[(alphaS)-alpha-[(1R)-2-[((3S,4aS,8aS)-3-(tert-butylcarbamoyl)octahydro-2(1H)-isoquinolinyl)-1-hydroxyethyl)phenethyl-2-quinaldamido]succinamide

2. 2(R)-Benzyl-5-(2(S)-(N-tert-butylcarbamoyl)-4-(3-pyridylmethyl)piperazin-1-yl)-4(S)-hydroxy-N-(2(R)-hydroxyindem-1(S)-yl)pentanamide

3. N-(Quinolin-2-ylcarbonyl)-asparagine-1(S)-benzyl-3-(3-tert-butyl-1-isobutylureido)-2(R)-hydroxypropylamide

4. N1-(2R-hydroxy-3-((3-methylbutyl)methylsulphonyl)amino)-1S-(phenylmethyl)propyl)-2S-((2-quinolinylcarbonyl)amino)butanediamide

5. (2S,3S,5S)-5(N-(N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

6. (R)-N-tert-butyl-3-((2S,3S)-2-hydroxy-3-N-((R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-methylthiopropanoyl)amino-4-phenylbutanoyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxamide

7. {3-[(4-Amino-benzenesulphonyl)-isobutyl-amino]-1-benzyl-2-hydroxypropyl}-carbamic acid tetrahydro-furan-3-yl ester

8. (3S,6R)-3-(α-Ethylbenzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one (VB 11 478, PCT WO 9411361)

9. N-[5-L-[N-(2-quinolinecarbonyl)-L-asparaginyl]amino-(4R,3S)-epoxy-6-phenyl-hexanoyl]-isoleucine

10. N-tert-butyl-1-[2-(R)-hydroxy-4-phenyl)-3(S)-[[N-(2-quinolinylcarbonyl)-asparaginyl]amino]butyl-4(R)-(phenylthio)piperidine-2(S)-carboxamide

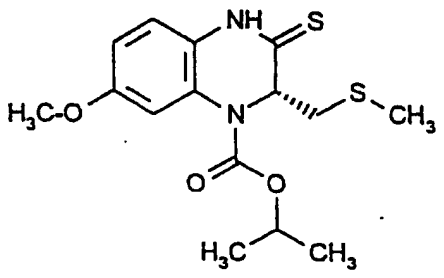
11. [3'''S-(3'''R*,4'''S*)]-N-[1'-oxo-1'-(3''-[1'''-oxo-2'''-aza-3'''-phenylmethyl-4'''-hydroxy-5'''-(2'''-N-tert-butylcarbamido)phenyl]pentyl-4''-methyl)-1,2,3,4-tetrahydroisoquinoline

12. 2-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenylsulphanylbutyl]-decahydro-isoquinoline-3-carboxylic acid tert-butylamide

13. 2H-1,4-Diazepin-2-one,hexahydro-6-hydroxy-1,3,4,7-tetrakis(phenylmethyl)-, [3S-(3.alpha, 6.beta, 7.beta)]

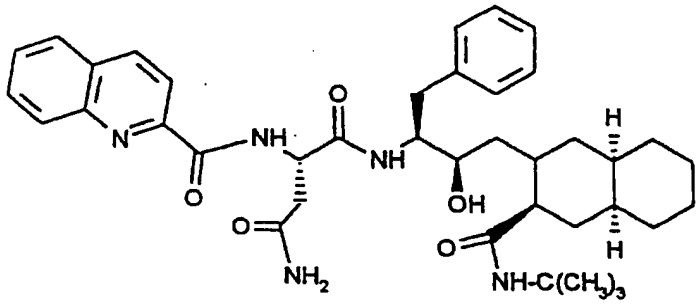
for use as medicaments in the treatment of AIDS and/or HIV infections.

The combination which is very particularly preferred for use in the control of AIDS and/or HIV infections is that of S-4-isopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxazolin-2(1H)-thione of the formula (A)



(A)

and (S)-N-[(alphaS)-alpha-[(1R)-2-[((3S,4aS,8aS)-3-(tert-butylcarbamoyl)-octahydro-2(1H)-isoquinolinyl)-1-hydroxyethyl)phenethyl-2-quinaldamido]-succinamide (Saquinavir) of the formula (B)



(B)

The quinoxalines of the general formulae (I) and (Ia) are known [cf. EP 509 398 A1]. The above-listed protease inhibitors are likewise known [cf. EP 432 695 A2, EP 569 083 A1, EP 541 168 A1, PCT WO 92/08688 A1, WO 92/08699 A1, WO 92/08698 A1, WO 92/08701 A1, WO 92/08700 A1, PCT WO 94/04492, PCT WO 94/14436, PCT WO 9411361, EP 601 486 A, EP 560 268 A, EP 609 625 A, PCT WO 94/08977].

The use of the combination of these compounds offers advantages, as compared with the monotherapy using the individual compounds, in the treatment of retrovirus-induced, in particular, however, HIV-induced, diseases. While the advantageous and superior employment of the combination of these compounds for treating AIDS infections or HIV infections is due in the main to the synergistic antiviral activity of the compounds, it is also due to the fact that the tolerability of the substances, when administered in combination, is unaltered, in the range of toxicity in which 50% of the cells survive, as compared with the tox-50 of the individual components. In the case of other combinations of compounds, for example AZT in combination with ganciclovir,

it is known that the use of these combinations results in synergistic toxicity [cf. M.N. Prichard et al.; Antimicrob. Agents Chemotherapy (1991), 35, 1060-1065].

In addition to this, the reduction in the effective dose which results from using the combination of the substances for the treatment diminishes the probability of the development of resistant virus isolates.

The invention deals with the combination of two classes of compound of the HIV reverse transcriptase and the HIV protease for preventing and treating infections with HIV and for treating the diseases, such as AIDS-related complex (ARC) or AIDS, which are induced by HIV.

HIV infection in cell culture

The HIV test was done according to the method of Pauwels et al. [cf. Journal of Virological Methods 20, (1988), 309 - 321]with slight modifications.

Normal human blood lymphocytes (PBL's) were enriched using Ficoll-Hypaque and stimulated with phytohaemagglutinin (90 µg/ml) and interleukin-2 (40 U/ml) in RPMI 1640 containing 20% foetal calf serum. For infection with the infectious HIV, the PBL's were pelleted and the cell pellet was then suspended, for adsorption, in 1 ml of HI virus solution, with this suspension being incubated at 37°C for 1 hour.

The virus adsorption solution was centrifuged and the infected cell pellet was taken up in growth medium at a cell density of 1×10^5 cells per ml. 1×10^4 cells which had been infected in this manner were pipetted into each of the wells of 96-well microtitre plates.
As an alternative, H9 cells were used for the antiviral tests in place of the PBL's.

The combined effect of the test substances was tested by means of chequerboard titration.
The first, vertical row of the microtitre plate contained only growth medium and cells which were not infected but which had otherwise been treated precisely as described

above (cell control). Only HIV infected cells (virus control) in growth medium were added to the second vertical row of the microtitre plate. The remaining wells contained the novel compounds - either alone or in appropriate combinations - in differing concentrations, proceeding from the wells of the 3rd vertical row of the microtitre plate, from which the test substances were further diluted in doubling-dilution steps (50 µl volume per well). In making the combinations, dilutions of the 2nd substance were prepared on a separate 96-well microtitre plate and then pipetted into the previously prepared first plate. 100 µl of the previously prepared HIV-infected cells (see above) were then added to each of these remaining wells. This resulted in test concentrations being covered within approximately the 10-50-fold range above and below the IC_{50} concentrations.

The test mixtures were incubated at 37°C until it was possible, using a microscope, to detect the syncytial formation which is typical for HIV in the host cells in the untreated virus control (between days 3 and 6 after infection). Under these test conditions, some 20-50 syncytia were obtained in the untreated virus control while no syncytia were present in the untreated cell control. The supernatants were then harvested from the 96-well plate and screened for HIV-specific antigen in an HIV-specific ELISA test (Vironostika HIV antigen, Organon Teknika).

The inhibition values were converted into per cent (%) inhibition values in accordance with the cut-off values from corresponding cell controls, virus controls or internal test controls, and the IC_{50} values were determined as the concentrations of the treated and infected cells at which 50% of the virus-specific antigen was suppressed by the treatment with the compounds. In order to analyse the synergistic activity of the compounds, the values for the differences between calculated and measured inhibition values were determined for each combination (Prichard, M.N. et al., Antimicrob. Agents Chemoth. (1993), 37, 540-545).

Difference values > zero denote that there was a synergistic effect. As an example, the following results were obtained:

Tab. 1 Table indicating the differences in the calculated and measured effects of saquinavir (B) together with the example of the formula (A)

Example of formula (A) nM	**50**	**25**	**12**	**6**	**3**	**1.5**	**0.7**
Saquinavir (B) nM							
50	0	0	0	13	32	30	16
25	0	0	0	29	49	20	3
12	0	0	0	37	40	0	0
6	0	0	0	32	57	23	0
3	0	0	0	27	0	0	0

Synergistic activity is obtained for the combinations within the concentration window of 0.7 - 6 nM for the example of the formula (A) and 6 - 50 nM for the protease inhibitor (B).

In order to measure the synergistic toxicity of the compounds, substance concentrations were tested which were around the tox-50 value of the individual compounds; the tests involved microscopic examination for cell-toxic features and vital staining using trypan blue. None of the combinations which was examined exhibited any synergistic toxicity.

It was found, surprisingly, that a synergistic effect on HIV is obtained by using the combination of the compounds. This was demonstrated, in an exemplary manner, by studies on the combination of the quinoxaline derivative and saquinavir (Tab. 1).

The novel combinations can be used in human and veterinary medicine for the treatment and prophylaxis of diseases which are caused by retroviruses.

The following may be mentioned, by way of example, as indications in human medicine:

1.) The treatment and prophylaxis of retroviral infections in humans.

2.) For the treatment or prophylaxis of diseases (AIDS), and the phases which are associated therewith, such as ARC (AIDS-related complex) and LAS (lymphadenopathy syndrome) which are caused by HIV I (human immunodeficiency virus; previously termed HTLV III/LAV), and also of the immune deficiency and encephalopathy which are caused by the virus.

3.) For the treatment or the prophylaxis of an HTLV-I or HTLV-II infection.

4.) For the treatment or the prophylaxis of the AIDS-carrier state.

The following may be listed, by way of example, as indications in veterinary medicine:

Infections with

a) maedivisna (in sheep and goats)

b) progressive pneumonia virus (PPV) (in sheep and goats)

c) caprine arthritis-encephalitis virus (in sheep and goats)

d) zwoegersiekte virus (in sheep)

e) infectious anaemia virus (of the horse)

f) infections which are caused by feline leukaemia virus

g) infections which are caused by feline immunodeficiency virus (FIV)

h) infections which are caused by simian immunodeficiency virus (SIV).

The human medicine indications listed in items 2, 3 and 4 above are preferred.

The present invention includes pharmaceutical preparations which, in addition to non-

toxic, inert, pharmaceutically suitable carrier substances, contain one or more compounds of the formulae (I) / (Ia) in combination with one of the given protease inhibitors, or which consist of one or more active compounds of the formulae (I) / (Ia) and the protease inhibitors, and also processes for producing these preparations, in particular the combination of the test compounds.

The active compounds of the formulae (I) and (Ia), and the protease inhibitors, are to be present in the above-listed pharmaceutical preparations at a concentration which is preferably from about 0.1 to 99.5 % by weight, preferably of from about 0.5 to 95% by weight, of the total mixture.

The above-listed pharmaceutical preparations can also contain further pharmaceutical active compounds in addition to the compounds of the formulae (I) / (Ia) in combination with one of the abovementioned protease inhibitors.

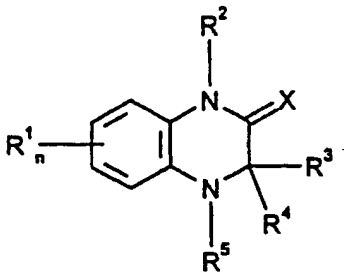
The above-listed pharmaceutical preparations are prepared in a customary manner using known methods, for example by mixing the active compound(s) with the carrier substance(s).

In general, it has been found to be advantageous, both in human and veterinary medicine, to administer the novel active compound(s) in total quantities of from about 0.5 to about 500, preferably of from 1 to 100, mg/kg of body weight every 24 hours, where appropriate in the form of several single doses, in order to achieve the desired results. A single dose preferably contains the active compound(s) in quantities of from about 1 to about 80, in particular of from 1 to 30, mg/kg of body weight. However, it may be necessary to deviate from the given dosages depending, specifically, on the nature and the body weight of the subject to be treated, on the nature and the severity of the disease, on the nature of the preparation and the administration of the medicament, and on the period of time and/or interval within which the administration takes place.

The invention also extends to a commercial package containing a protease inhibitor and a quinoxaline of formula (I) or (Ia), together with instructions for their use in the treatment or prophylaxis of retroviral infections in human or veterinary medicine.

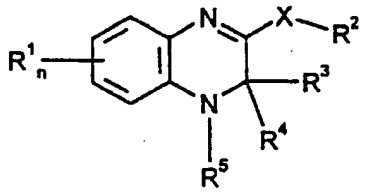
Patent Claims

1. Medicament which contains, in combination, one or more protease inhibitors and one or more of the quinoxalines of the general formula (I) and (Ia)



(I)

and also their tautomeric forms of the general formula Ia



(Ia)

in which

1) n is zero,
one,
two,
three
or four,

the individual substituents R^1 are, independently of each other,

fluorine, chlorine, bromine, iodine, trifluoromethyl, trifluoromethoxy, hydroxyl, C_1-C_8-alkyl, C_5-C_8-cycloalkyl, C_1-C_6-alkoxy, (C_1-C_6-alkoxy)-(C_1-C_4-alkoxy), C_1-C_6-alkylthio, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, nitro, amino, azido, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, piperidino, morpholino, 1-pyrrolidinyl, 4-methylpiperazinyl, thiomorpholino, imidazolyl, triazolyl, tetrazolyl, C_1-C_6-acyl, C_1-C_6-acyloxy, C_1-C_6-acylamino, cyano, carbamoyl, carboxyl, (C_1-C_6-alkyl)-

phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-allenyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_3-C_8-alkinyl,
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-cycloalkyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-cycloalkenyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

(C_3-C_8-cycloalkyl)-(C_1-C_4-alkyl)
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

(C_3-C_8-cycloalkenyl)-(C_1-C_4-alkyl)

which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_1-C_6-alkylcarbonyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_6-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_6-alkoxy, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, phenylsulphonyl, oxo, thioxo, carboxyl or carbamoyl;

C_2-C_8-alkenylcarbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_3-C_8-cycloalkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_5-C_8-cycloalkenyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_3-C_8-cycloalkyl)-(C_1-C_3-alkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_5-C_6-cycloalkenyl)-(C_1-C_3-alkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_8-alkyloxycarbonyl which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino or C_1-C_4-alkylthio;

C_2-C_8-alkenyloxycarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_2-C_8-alkinyloxycarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_8-alkylthiocarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_2-C_8-alkenylthiocarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_8-alkylaminocarbonyl and di(C_1-C_8-alkyl)aminocarbonyl which are optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

pyrrolidin-1-yl, morpholino-, piperidino-, piperazinyl- or 4-methylpiperazin-1-yl-carbonyl which are optionally substituted by C_1-C_4-alkyl, C_2-C_6-alkenyl, C_1-C_4-acyl, oxo, thioxo, carboxyl or phenyl;

C_2-C_8-alkenylaminocarbonyl and di(C_1-C_6-alkenyl)aminocarbonyl which are optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_6-alkylsulphonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_6-alkenylsulphonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

or aryl, arylcarbonyl, aryl(thiocarbonyl), (arylthio)carbonyl, (arylthio)thiocarbonyl, aryloxycarbonyl, arylaminocarbonyl, (arylamino)thiocarbonyl, arylalkylaminocarbonyl, arylsulphonyl,

arylalkyl, arylalkenyl, arylalkinyl, arylalkylcarbonyl, arylalkenylcarbonyl, arylalkoxycarbonyl or aryl(alkylthio)carbonyl which are substituted by up to five R^6 radicals which are independent of each other, and where the alkyl radical can in each case contain from 1 to 5 C atoms and R^6 is defined as above

or heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkylcarbonyl or heteroarylalkenylcarbonyl, heteroaryloxycarbonyl, (heteroarylthio)carbonyl, heteroarylaminocarbonyl, heteroarylalkyloxycarbonyl, heteroaryl(alkylthio)carbonyl or heteroarylalkylaminocarbonyl which are substituted by up to three R^6 radicals which are independent of each other, and where the alkyl radical can in each case contain from 1 to 3 C atoms,

R^3 and R^4 are identical or different and are, independently of each other,

hydrogen, or C_1-C_8-alkyl which is optionally substituted by fluorine, chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_2-C_8-alkenyl which is optionally substituted by fluorine or chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_3-C_8-cycloalkyl which is optionally substituted by fluorine, chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_3-C_8-cycloalkenyl which is optionally substituted by fluorine or chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;
aryl, arylalkyl, heteroaryl or heteroarylalkyl which are substituted by up to five R^6 radicals which are independent of each other, and where the alkyl radical can in each case contain from 1 to 3 C atoms and R^6 is defined as above,

R^3 and R^4 or R^3 and R^5 can, in addition, also be part of a saturated or unsaturated carbocyclic or heterocyclic ring having from 3 to 8 C atoms which can optionally be substituted by fluorine, chlorine, hydroxyl, amino, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_1-C_6-acyloxy, benzoyloxy, C_1-C_6-alkoxy, oxo, thioxo, carboxyl, carbamoyl or phenyl,

X denotes oxygen, sulphur, selenium or substituted nitrogen N-R^2, in which R^2 can have the abovementioned meanings,

with the exception of the compounds in which R^3 and R^4 simultaneously denote H and compounds in which R^2 and R^5 denote H and R^3 and/or R^4 denote arylalkyl and compounds in which X denotes oxygen and R^2 and R^5 denote hydrogen.

2. Medicament according to Claim 1, which contains one or more of the quinoxalines of the general formula (I) and (Ia),

in which

2) n is zero,
one,
two
or three,

the individual substituents R^1 are, independently of each other,

fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, hydroxyl, C_1-C_4-alkyl, C_5-C_6-cycloalkyl, C_1-C_4-alkoxy, (C_1-C_4-alkoxy)-(C_1-C_4-alkoxy), C_1-C_4-alkylthio, C_1-C_4-alkyl-sulphinyl, C_1-C_4-alkylsulphonyl, nitro, amino, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, piperidino, morpholino, 1-pyrrolidinyl, 4-methyl-piperazinyl, thiomorpholino, imidazolyl, C_1-C_4-acyl, C_1-C_4-acyloxy, C_1-C_4-acylamino, cyano, carbamoyl, carboxyl, (C_1-C_4-alkyl)-oxycarbonyl, hydroxysulphonyl or sulphamoyl,

or

are a phenyl, phenoxy, phenoxycarbonyl, phenylthio, phenylsulphinyl, phenylsulphonyl, phenoxy-sulphonyl, phenylsulphonyloxy, anilinosulphonyl, phenylsulphonylamino, benzoyl, 2-pyridyl, 3-pyridyl or 4-pyridyl radical which is substituted by up to two R^6 radicals which are independent of each other,

where R^6

can be fluorine, chlorine, bromine, cyano, trifluoromethyl, nitro, amino, C_1-C_4-alkyl, C_3-C_7-cycloalkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, C_1-C_4-alkyl-sulphinyl, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)-amino, (C_1-C_4-alkyl)-oxycarbonyl, phenyl or phenoxy,

R^2 is hydrogen and R^5 is

hydrogen, hydroxyl, cyano, amino, C_1-C_6-alkyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl

or carbamoyl;

C_2-C_8-alkenyl,
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-allenyl,

C_3-C_8-alkinyl,
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-cycloalkyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_3-C_8-cycloalkenyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

(C_3-C_8-cycloalkyl)-(C_1-C_2-alkyl)
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

(C_3-C_8-cycloalkenyl)-(C_1-C_2-alkyl)
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_1-C_6-alkylcarbonyl
which is optionally substituted by
fluorine, chlorine, bromine, iodine, cyano, amino, mercapto, hydroxyl, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, oxo, thioxo, carboxyl or carbamoyl;

C_2-C_6-alkenylcarbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_3-C_6-cycloalkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_5-C_6-cycloalkenyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_3-C_6-cycloalkyl)-(C_1-C_2-alkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

(C_5-C_6-cycloalkenyl)-(C_1-C_2-alkyl)carbonyl which is optionally substituted by fluorine, chlorine or hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_6-alkyloxycarbonyl which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino or C_1-C_4-alkylthio;

C_2-C_6-alkenyloxycarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_2-C_6-alkinyloxycarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_6-alkylthiocarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_2-C_6-alkenylthiocarbonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_6-alkylaminocarbonyl and di(C_1-C_6-alkyl)aminocarbonyl which are optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

pyrrolidin-1-yl or morpholino-, piperidino-, piperazinyl- or 4-methylpiperazin-1-yl-carbonyl;

C_2-C_6-alkenylaminocarbonyl and di(C_1-C_6-alkenyl)aminocarbonyl which are optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_4-alkylsulphonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

C_1-C_4-alkenylsulphonyl which is optionally substituted by fluorine, chlorine, hydroxyl, C_1-C_4-alkoxy, oxo or phenyl;

or aryl, arylcarbonyl, aryl(thiocarbonyl), (arylthio)carbonyl, (arylthio)thiocarbonyl, aryloxycarbonyl, arylaminocarbonyl, (arylamino)thiocarbonyl, arylalkylaminocarbonyl, arylsulphonyl, arylalkyl, arylalkenyl, arylalkinyl, arylalkylcarbonyl, arylalkenylcarbonyl, aryl(alkylthio)carbonyl or arylalkoxycarbonyl which are substituted by up to three R^6 radicals which are independent of each other and where the alkyl radical can in each case contain from 1 to 5 C atoms and R^6 is defined as above

or 1- or 2-naphthylmethyl, 2-, 3- or 4-picolyl, 2- or 3-furylmethyl, 2- or 3-thienylmethyl, 2- or 3-pyrrolylmethyl, 2-, 3- or 4-pyridylcarbonyl, 2- or 3-furylcarbonyl, 2- or 3-thienylcarbonyl, 2- or 3-thienylacetyl, 2-, 3- or 4-picolyloxycarbonyl, 2- or 3-furylmethyloxycarbonyl or 2- or 3-thienylmethyloxycarbonyl which are substituted by up to two R^6 radicals which are independent of each other,

and

R^3 and R^4 are identical or different and are, independently of each other,

hydrogen,

C_1-C_6-alkyl

which is optionally substituted by fluorine, chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_2-C_8-alkenyl which is optionally substituted by fluorine or chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-

alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_3-C_8-cycloalkyl which is optionally substituted by fluorine, chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_3-C_8-cycloalkenyl which is optionally substituted by fluorine or chlorine, hydroxyl, amino, mercapto, C_1-C_4-acyloxy, benzoyloxy, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;
or aryl, arylalkyl, heteroaryl or heteroarylalkyl which are substituted by up to three R^6 radicals which are independent of each other, and where the alkyl radical can in each case contain from 1 to 3 C atoms and R^6 is defined as above,

R^3 and R^4 can, in addition, also be

part of a saturated or unsaturated carbocyclic or heterocyclic ring having from 3 to 7 C atoms which can optionally be substituted by fluorine, chlorine, hydroxyl, amino, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkinyl, C_1-C_4-acyloxy, benzoyloxy, C_1-C_4-alkoxy, oxo, thioxo, carboxyl, carbamoyl or phenyl,

X denotes oxygen, sulphur or selenium

optionally in an isomeric form.

3. Medicament according to Claim 1, which contains one or more quinoxalines of the general formulae (I) and (Ia),

in which

n is zero,
one
or two,

the individual substituents R^1 are, independently of each other,

fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, (C_1-C_4-alkoxy)-(C_1-C_2-alkoxy), C_1-C_4-alkylthio, nitro, amino, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino, piperidino, morpholino, 1-pyrrolidinyl, 4-methylpiperazinyl, C_1-C_4-acyl, C_1-C_4-acyloxy, C_1-C_4-acylamino, cyano, carbamoyl, carboxyl, (C_1-C_4-alkyl)-oxycarbonyl, hydroxysulphonyl or sulphamoyl,

or

are a phenyl, phenoxy, phenylthio, phenylsulphonyl, phenoxysulphonyl, benzoyl, 2-pyridyl, 3-pyridyl or 4-pyridyl radical which is substituted by up to two R^6 radicals which are independent of each other,

where R^6 can be

fluorine, chlorine, bromine, cyano, trifluoromethyl, nitro, amino, C_1-C_4-alkyl, C_1-C_4-alkoxy, (C_1-C_4-alkyl)-oxycarbonyl, phenyl or phenoxy,

R^2 is hydrogen and R^5 is

C_1-C_6-alkyl
which is optionally substituted by C_1-C_4-alkoxy or C_1-C_4-alkylthio;

C_2-C_6-alkenyl,
which is optionally substituted by oxo;

C_3-C_6-allenyl,

C_3-C_8-alkinyl, in particular 2-butinyl;

C_3-C_6-cycloalkyl;

C_5-C_6-cycloalkenyl;

(C_3-C_6-cycloalkyl)-(C_1-C_2-alkyl), in particular cyclopropylmethyl, which is optionally substituted by C_1-C_4-alkyl;

(C_3-C_6-cycloalkenyl)-(C_1-C_2-alkyl), in particular cyclohexenylmethyl;

C_1-C_6-alkylcarbonyl
which is optionally substituted by fluorine, chlorine, hydroxyl, benzyloxy, phenoxy, C_1-C_4-alkoxy, C_1-C_4-alkylamino, C_1-C_4-alkenylamino, di(C_1-C_4-alkyl)amino, 1-pyrrolidinyl, piperidino, morpholino, 4-methylpiperazin-1-yl or C_1-C_4-alkylthio;

C_2-C_6-alkenylcarbonyl;

C_1-C_6-alkyloxycarbonyl which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, C_1-C_4-alkoxy, C_1-C_4-alkylamino, di(C_1-C_4-alkyl)amino or C_1-C_4-alkylthio;

C_2-C_6-alkenyloxycarbonyl, in particular vinyloxycarbonyl, allyloxycarbonyl, isopropenyloxycarbonyl, butenyloxycarbonyl or pentenyloxycarbonyl;

C_2-C_6-alkinyloxycarbonyl, in particular propinyloxycarbonyl or butinyloxycarbonyl;

C_1-C_6-alkylthiocarbonyl;

C_2-C_6-alkenylthiocarbonyl, in particular allylthiocarbonyl;

C_1-C_6-alkylaminocarbonyl and di(C_1-C_6-alkyl)aminocarbonyl;

pyrrolidin-1-yl or morpholino-, piperidino-, piperazinyl- or 4-methylpiperazin-1-yl-carbonyl;

C_2-C_6-alkenylaminocarbonyl and di(C_1-C_6-alkenyl)aminocarbonyl;

C_1-C_4-alkylsulphonyl;

C_1-C_4-alkenylsulphonyl;

or aryl, in particular phenyl,
arylcarbonyl, in particular benzoyl, (arylthio)carbonyl, aryloxycarbonyl, arylaminocarbonyl, (arylamino)thiocarbonyl, arylalkylaminocarbonyl, arylsulphonyl,
arylalkyl, in particular benzyl, phenylethyl, arylalkenyl, arylalkylcarbonyl, arylalkoxycarbonyl or aryl(alkylthio)carbonyl which are substituted by up to two R^6 radicals which are independent of each other and where the alkyl radical can in each case contain from 1 to 3 C atoms and R^6 is defined as above

or 1- or 2-naphthylmethyl, 2-, 3- or 4-picolyl, 2- or 3-furylmethyl, 2- or 3-thienylmethyl, 2- or 3-pyrrolylmethyl, 2-, 3- or 4-pyridylcarbonyl, 2- or 3-furylcarbonyl, 2- or 3-thienylcarbonyl, 2- or 3-thienylacetyl, 2-, 3- or 4-picolyloxycarbonyl, 2- or 3-furylmethyloxycarbonyl or 2- or 3-thienylmethyloxycaronyl which are substituted by up to two R^6 radicals which are independent of each other,

and

R^3 and R^4 are identical or different and are, independently of each other,

hydrogen,

C_1-C_4-alkyl

which is optionally substituted by hydroxyl, mercapto, C_1-C_4-alkoxy, C_1-C_4-alkylthio, C_1-C_4-alkylsulphonyl, C_1-C_4-alkylsulphinyl, carboxyl or carbamoyl;

C_2-C_6-alkenyl,

aryl, benzyl, thienyl or thienylmethyl which are substituted by up to two R^6 radicals which are independent of each other and where R^6 is defined as above,

R^3 and R^4 can also be

part of a saturated or unsaturated carbocyclic or heterocyclic ring having from 3 to 6 C atoms which can optionally be substituted by oxo or thioxo, and

X denotes oxygen or sulphur

optionally in an isomeric form.

4. Medicament according to Claims 1 to 3, which contains, as protease inhibitor, one or more compounds from the group

1. (S)-N-[(alphaS)-alpha-[(1R)-2-[((3S,4aS,8aS)-3-(tert-butylcarbamoyl)octahydro-2(1H)-isoquinolinyl)-1-hydroxyethyl)phenethyl-2-quinaldamido]succinamide

2. 2(R)-Benzyl-5-(2(S)-(N-tert-butylcarbamoyl)-4-(3-pyridylmethyl)piperazin-1-yl)-4(S)-hydroxy-N-(2(R)-hydroxyindem-1(S)-yl)pentanamide

3. N-(Quinolin-2-ylcarbonyl)-asparagine-1(S)-benzyl-3-(3-tert-butyl-1-isobutylureido)-2(R)-hydroxypropylamide

4. N1-(2R-hydroxy-3-((3-methylbutyl)methylsulphonyl)amino)-1S-(phenylmethyl)propyl)-2S-((2-quinolinylcarbonyl)amino)butanediamide

5. (2S,3S,5S)-5(N-(N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

6. (R)-N-tert-butyl-3-((2S,3S)-2-hydroxy-3-N-((R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-methylthiopropanoyl)amino-4-phenylbutanoyl)-5,5-dimethyl-1,3-thiazolidine-4-carboxamide

7. {3-[(4-Amino-benzenesulphonyl)-isobutyl-amino]-1-benzyl-2-hydroxypropyl}-carbamic acid tetrahydro-furan-3-yl ester

8. (3S,6R)-3-(α-Ethylbenzyl)-6-(α-ethylphenethyl)-4-hydroxy-2H-pyran-2-one (VB 11 478, PCT WO 9411361)

9. N-[5-L-[N-(2-quinolinecarbonyl)-L-asparaginyl]amino-(4R,3S)-epoxy-6-phenyl-hexanoyl]-isoleucine

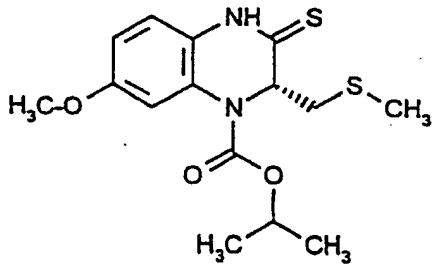
10. N-tert-butyl-1-[2-(R)-hydroxy-4-phenyl)-3(S)-[[N-(2-quinolinylcarbonyl)-asparaginyl]amino]butyl-4(R)-(phenylthio)piperidine-2(S)-carboxamide

11. [3'''S-(3'''R*,4'''S*)]-N-[1'-oxo-1'-(3''-[1'''-oxo-2'''-aza-3'''-phenylmethyl-4'''-hydroxy-5'''-(2'''-N-tert-butylcarbamido)phenyl]pentyl-4''-methyl)-1,2,3,4-tetrahydroisoquinoline

12. 2-[2-Hydroxy-3-(3-hydroxy-2-methyl-benzoylamino)-4-phenylsulphanylbutyl]-decahydro-isoquinoline-3-carboxylic acid tert-butylamide

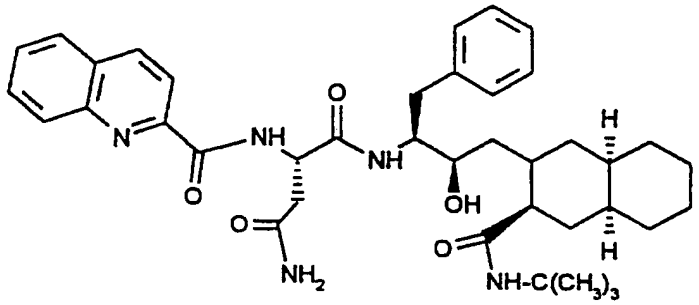
13. 2H-1,4-Diazepin-2-one,hexahydro-6-hydroxy-1,3,4,7-tetrakis(phenylmethyl)-, [3S-(3.alpha, 6.beta, 7.beta)].

5. Medicament which contains, in combination S-4-isopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxazolin-2(1H)-thione of the formula (A)



(A)

and (S)-N-[(alphaS)-alpha-[(1R)-2-[((3S,4aS,8aS)-3-(tert-butylcarbamoyl)-octahydro-2(1H)-isoquinolinyl)-1-hydroxyethyl)phenethyl-2-quinaldamido]-succinamide (Saquinavir) of the formula (B)



(B).

6. Use of a protease inhibitor and a quinoxaline of the general formula (I) or (Ia) as defined in any one of Claims 1 to 3 for the treatment or prophylaxis of retroviral infections in humans.

7. Use of a protease inhibitor and a quinoxaline of the general formula (I) or (Ia) as defined in any one of Claims 1 to 3 for the treatment or prophylaxis of AIDS and the phases associated therewith.

8. Use of a protease inhibitor and a quinoxaline of the general formula (I) or (Ia) as defined in any one of Claims 1 to 3 for the treatment or prophylaxis of an HTLV-I or HTLV-II infection.

9. Use of a protease inhibitor and a quinoxaline of the general formula (I) or (Ia) as defined in any one of Claims 1 to 3 for the treatment or prophylaxis of the AIDS-carrier state.

10. Use of a protease inhibitor and a quinoxaline of the general formula (I) or (Ia) as defined in any one of Claims 1 to 3 for the treatment or prophylaxis of infections caused by maedivisna (in sheep and goats), progressive pneumonia virus (PPV) (in sheep and goats), caprine arthritis-encephalitis virus (in sheep and goats), zwoegersiekte virus (in sheep), infectious anaemia virus (of the horse), feline leukaemia virus, feline immunodeficiency virus (FIV) and simian immunodeficiency virus (SIV) in veterinary medicine.

11. Use according to any one of Claims 6 to 10 wherein the protease inhibitor is selected from the group of protease inhibitors defined in Claim 4.

12. Use according to any one of Claims 6 to 10 wherein the protease inhibitor is (S)-N-[(alphaS)-alpha-[(1R)-2-[((3S,4aS,8aS)-3-(tert-butylcarbamoyl)octahydro-2(1H)-isoquinolinyl)-1-hydroxyethyl)phenethyl-2-quinaldamido]-succinamide (Saquinavir) and the compound of formula (I) or (Ia) is S-4-isopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxazolin-2(1H)-thione.

13. Use according to any one of Claims 6 to 10 wherein the protease inhibitor and the quinoxaline of formula (I) or (Ia) are present in combination in the same medicament composition.

14. A process for preparing a medicament for use in treatment or prophylaxis of retroviral infections in human or veterinary medicine, which process comprises admixing a quinoxaline of the general formula (I) or (Ia) as defined in any one of Claims 1 to 3, with a protease inhibitor.

15. A process according to Claim 14 wherein the protease inhibitor is selected from the group of protease inhibitors defined in Claim 4.

16. A process according to Claim 14 wherein the protease inhibitor is (S)-N-[(alphaS)-alpha-[(IR)-2-[((3S,4aS,8aS)-3-(tert-butylcarbamoyl)octahydro-2(1H)-

isoquinolinyl)-1-hydroxyethyl)phenethyl-2-quinaldamido]-succinamide (Saquinavir) and the compound of formula (I) or (Ia) is S-4-isopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxazolin-2(1H)-thione.

17. A process according to any one of Claims 14 to 16 wherein a pharmaceutically acceptable diluent or carrier is included in the medicament.

18. A commercial package containing a protease inhibitor and a quinoxaline of the general formula (I) or (Ia) as defined in any one of Claims 1 to 3, together with instructions for its use in the treatment or prophylaxis of retroviral infections in human or veterinary medicine.

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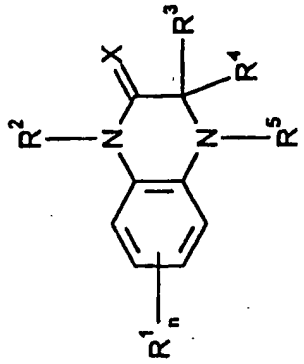
X
R3
R4
R2
N
N
R5
R1n